SDHB gene

succinate dehydrogenase complex iron sulfur subunit B

Normal Function

The *SDHB* gene provides instructions for making one of four subunits of the succinate dehydrogenase (SDH) enzyme. The SDH enzyme plays a critical role in mitochondria, which are structures inside cells that convert the energy from food into a form that cells can use.

Within mitochondria, the SDH enzyme links two important pathways in energy conversion: the citric acid cycle (or Krebs cycle) and oxidative phosphorylation. As part of the citric acid cycle, the SDH enzyme converts a compound called succinate to another compound called fumarate. Negatively charged particles called electrons are released during this reaction. The SDHB protein provides an attachment site for electrons as they are transferred to the oxidative phosphorylation pathway. In oxidative phosphorylation, the electrons help create an electrical charge that provides energy for the production of adenosine triphosphate (ATP), the cell's main energy source.

Succinate, the compound on which the SDH enzyme acts, is an oxygen sensor in the cell and can help turn on specific pathways that stimulate cells to grow in a low-oxygen environment (hypoxia). In particular, succinate stabilizes a protein called hypoxia-inducible factor (HIF) by preventing a reaction that would allow HIF to be broken down. HIF controls several important genes involved in cell division and the formation of new blood vessels in a hypoxic environment.

The *SDHB* gene is a tumor suppressor, which means it prevents cells from growing and dividing in an uncontrolled way.

Health Conditions Related to Genetic Changes

Cowden syndrome

At least 10 variants in the *SDHB* gene have been identified in people with Cowden syndrome or a similar disorder called Cowden-like syndrome. These conditions are characterized by multiple tumor-like growths called hamartomas and an increased risk of developing certain cancers, particularly breast cancer, thyroid cancer, and cancer of the uterine lining (endometrial cancer).

The *SDHB* gene variants associated with Cowden syndrome and Cowden-like syndrome change single amino acids in the SDHB protein, which likely alters the function of the SDH enzyme. Studies suggest that the defective enzyme could allow cells to grow and divide unchecked, leading to the formation of hamartomas and

cancerous tumors. However, researchers are uncertain whether the identified *SDHB* gene variants are directly associated with Cowden syndrome and Cowden-like syndrome. Some of the variants described above have rarely been found in people without the features of these conditions.

gastrointestinal stromal tumor

hereditary paraganglioma-pheochromocytoma

More than 150 mutations in the *SDHB* gene have been identified in people with hereditary paraganglioma-pheochromocytoma type 4. People with this condition have paragangliomas, pheochromocytomas, or both. Paragangliomas and pheochromocytomas (a type of paraganglioma) are noncancerous tumors associated with the nervous system. An inherited *SDHB* gene mutation predisposes an individual to the condition, and a somatic mutation that deletes the normal copy of the gene is needed to cause hereditary paraganglioma-pheochromocytoma type 4.

Most of the inherited *SDHB* gene mutations change single protein building blocks (amino acids) in the SDHB protein sequence or result in a shortened protein. As a result, there is little or no SDH enzyme activity. Because the mutated SDH enzyme cannot convert succinate to fumarate, succinate accumulates in the cell. The excess succinate abnormally stabilizes HIF, which also builds up in cells. Excess HIF stimulates cells to divide and triggers the production of blood vessels when they are not needed. Rapid and uncontrolled cell division, along with the formation of new blood vessels, can lead to the development of tumors in people with hereditary paraganglioma-pheochromocytoma.

nonsyndromic paraganglioma

Mutations in the *SDHB* gene are found in some cases of nonsyndromic paraganglioma or pheochromocytoma, which are non-hereditary forms of the condition. Most of these mutations change single amino acids in the SDHB protein. As in hereditary paraganglioma-pheochromocytoma type 4, these mutations are expected to decrease SDH enzyme activity, which stabilizes the HIF protein, causing it to build up in cells. Excess HIF protein abnormally stimulates cell division and the formation of blood vessels, which can lead to tumor formation.

other cancers

The *SDHB* gene is involved in several cancers. Mutations in the *SDHB* gene have been found in a small number of people with gastrointestinal stromal tumors (GISTs), which are a type of tumor that occurs in the gastrointestinal tract, or renal cell carcinoma, which is a type of kidney cancer. *SDHB* gene mutations have been identified in people a condition called Carney-Stratakis syndrome in which affected individuals have both paraganglioma and GIST or in people with both renal cell cancer and paraganglioma. An inherited *SDHB* gene mutation predisposes

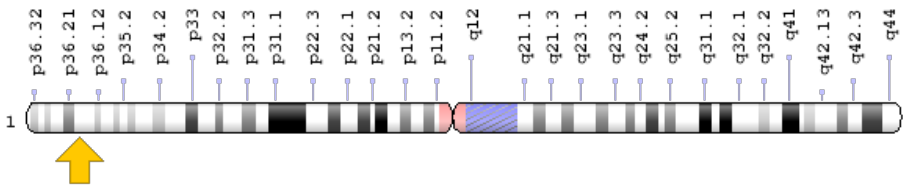
an individual to cancer formation. An additional mutation that deletes the normal copy of the gene is needed to cause these forms of GIST, renal cell cancer, and paraganglioma. This second mutation, called a somatic mutation, is acquired during a person's lifetime and is present only in tumor cells.

Mutations of the *SDHB* gene lead to a reduction in the amount of SDHB protein in the cell and loss of SDH enzyme activity. Furthermore, even without a *SDHB* gene mutation, a subset of gastrointestinal stromal tumors have reduced SDHB protein and loss of SDH enzyme activity. Lack of SDH enzyme activity results in abnormal hypoxia signaling and formation of tumors.

Chromosomal Location

Cytogenetic Location: 1p36.13, which is the short (p) arm of chromosome 1 at position 36.13

Molecular Location: base pairs 17,018,722 to 17,054,170 on chromosome 1 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- DHSB_HUMAN
- FLJ92337
- IP
- iron-sulfur subunit of complex II
- PGL4
- SDH
- SDH1
- SDH2
- SDHIP
- succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial

- succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial precursor
- succinate dehydrogenase complex subunit B, iron sulfur (Ip)
- succinate dehydrogenase complex, subunit B, iron sulfur (Ip)

Additional Information & Resources

Educational Resources

- Biochemistry (5th Edition, 2002): Oxaloacetate Is Regenerated by the Oxidation of Succinate
  https://www.ncbi.nlm.nih.gov/books/NBK22427/#A2401

GeneReviews

- Hereditary Paraganglioma-Pheochromocytoma Syndromes
  https://www.ncbi.nlm.nih.gov/books/NBK1548

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28SDHB%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- GASTROINTESTINAL STROMAL TUMOR
  http://omim.org/entry/606764
- PARAGANGLIOMA AND GASTRIC STROMAL SARCOMA
  http://omim.org/entry/606864
- SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT B, IRON SULFUR PROTEIN
  http://omim.org/entry/185470

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/SDHBID388.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=SDHB%5Bgene%5D
- HGNC Gene Family: Mitochondrial complex II: succinate dehydrogenase subunits
  http://www.genenames.org/cgi-bin/genefamilies/set/641

- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=10681
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/6390
- UniProt
  http://www.uniprot.org/uniprot/P21912

Sources for This Summary

- Astuti D, Latif F, Dallol A, Dahia PL, Douglas F, George E, Sköldberg F, Husebye ES, Eng C, Maher ER. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. Am J Hum Genet. 2001 Jul;69(1):49-54. Epub 2001 Jun 12. Erratum in: Am J Hum Genet 2002 Feb;70(2):565.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11404820
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1226047/
- Burnichon N, Rohmer V, Amar L, Herman P, Leboulleux S, Darrouzet V, Niccoli P, Gaillard D, Chabrier G, Chabolle F, Coupier I, Thieblot P, Lecomte P, Bertherat J, Wion-Barbot N, Murat A, Venisse A, Plouin PF, Jeunemaitre X, Gimenez-Roqueplo AP; PGL.NET network. The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. J Clin Endocrinol Metab. 2009 Aug;94(8):2817-27. doi: 10.1210/jc.2008-2504. Epub 2009 May 19.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19454582
- Gill AJ, Pachter NS, Clarkson A, Tucker KM, Winship IM, Benn DE, Robinson BG, Clifton-Bligh RJ. Renal tumors and hereditary pheochromocytoma-paraganglioma syndrome type 4. N Engl J Med. 2011 Mar 3;364(9):885-6. doi: 10.1056/NEJMc1012357.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21366490
- Janeway KA, Kim SY, Lodish M, Nosé V, Rustin P, Gaal J, Dahia PL, Liegl B, Ball ER, Raygada M, Lai AH, Kelly L, Hornick JL; NIH Pediatric and Wild-Type GIST Clinic, O'Sullivan M, de Krijger RR, Dinjens WN, Demetri GD, Antonescu CR, Fletcher JA, Helman L, Stratakis CA. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A. 2011 Jan 4;108(1):314-8. doi: 10.1073/pnas.1009199108. Epub 2010 Dec 20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21173220
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3017134/
- Müller U. Pathological mechanisms and parent-of-origin effects in hereditary paraganglioma/pheochromocytoma (PGL/PCC). Neurogenetics. 2011 Aug;12(3):175-81. doi: 10.1007/s10048-011-0280-y. Epub 2011 Mar 9. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21547462
- Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Altehoefer C, Zerres K, Januszewicz A, Eng C, Smith WM, Munk R, Manz T, Glaesker S, Apel TW, Treier M, Reineke M, Walz MK, Hoang-Vu C, Brauckhoff M, Klein-Franke A, Klose P, Schmidt H, Maier-Woelfle M, Peçzkowska M, Szmigielski C, Eng C; Freiburg-Warsaw-Columbus Pheochromocytoma Study Group. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med. 2002 May 9;346(19):1459-66.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12000816

- Ni Y, He X, Chen J, Moline J, Mester J, Orloff MS, Ringel MD, Eng C. Germline SDHx variants modify breast and thyroid cancer risks in Cowden and Cowden-like syndrome via FAD/NAD-dependant destabilization of p53. Hum Mol Genet. 2012 Jan 15;21(2):300-10. doi: 10.1093/hmg/ddr459. Epub 2011 Oct 6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21979946
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3276278/
- Ni Y, Zbuk KM, Sadler T, Patocs A, Lobo G, Edelman E, Platzer P, Orloff MS, Waite KA, Eng C. Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes. Am J Hum Genet. 2008 Aug;83(2):261-8. doi: 10.1016/j.ajhg.2008.07.011.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18678321
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2495063/
- Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, Boikos SA, Ferrando B, Pacak K, Assie G, Baudin E, Chompret A, Ellison JW, Briere JJ, Rustin P, Gimenez-Roqueplo AP, Eng C, Carney JA, Stratakis CA. Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. Eur J Hum Genet. 2008 Jan;16(1):79-88. Epub 2007 Aug 1.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17667967
- Pasini B, Stratakis CA. SDH mutations in tumorigenesis and inherited endocrine tumours: lesson from the phaeochromocytoma-paraganglioma syndromes. J Intern Med. 2009 Jul;266(1):19-42. doi: 10.1111/j.1365-2796.2009.02111.x. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19522823
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3163304/
- Pollard PJ, Brière JJ, Alam NA, Barwell J, Barclay E, Wortham NC, Hunt T, Mitchell M, Olpin S, Moat SJ, Hargreaves IP, Heales SJ, Chung YL, Griffiths JR, Dalgleish A, McGrath JA, Gleeson MJ, Hodgson SV, Poulsom R, Rustin P, Tomlinson IP. Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. Hum Mol Genet. 2005 Aug 1;14(15):2231-9. Epub 2005 Jun 29.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15987702
- Ricketts C, Woodward ER, Killick P, Morris MR, Astuti D, Latif F, Maher ER. Germline SDHB mutations and familial renal cell carcinoma. J Natl Cancer Inst. 2008 Sep 3;100(17):1260-2. doi: 10.1093/jnci/djn254. Epub 2008 Aug 26.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18728283
- OMIM: SUCCINATE DEHYDROGENASE COMPLEX, SUBUNIT B, IRON SULFUR PROTEIN http://omim.org/entry/185470
- Selak MA, Armour SM, MacKenzie ED, Boulahbel H, Watson DG, Mansfield KD, Pan Y, Simon MC, Thompson CB, Gottlieb E. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. Cancer Cell. 2005 Jan;7(1):77-85.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15652751

- Stratakis CA, Carney JA. The triad of paragangliomas, gastric stromal tumours and pulmonary chondromas (Carney triad), and the dyad of paragangliomas and gastric stromal sarcomas (Carney-Stratakis syndrome): molecular genetics and clinical implications. J Intern Med. 2009 Jul;266(1): 43-52. doi: 10.1111/j.1365-2796.2009.02110.x. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19522824
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3129547/
- Vanharanta S, Buchta M, McWhinney SR, Virta SK, Peçzkowska M, Morrison CD, Lehtonen R, Januszewicz A, Järvinen H, Juhola M, Mecklin JP, Pukkala E, Herva R, Kiuru M, Nupponen NN, Aaltonen LA, Neumann HP, Eng C. Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma. Am J Hum Genet. 2004 Jan;74(1):153-9. Epub 2003 Dec 18.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14685938
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1181902/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/SDHB

Reviewed: October 2012
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services